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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/004,115	12/06/2001	Hiroyuki Asako	7372-72249	3895

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,115	ASAKO ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004, 13 February 2004 and* 25 February 2004.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-41* is/are pending in the application.

4a) Of the above claim(s) *15-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-14 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed February 6, 2004 amending claims 1, 4, 8, 9, 11, 14, 16, 19-21, 23 and 26-38, canceling claim 10 and adding claims 39-41 has been entered.

The amendment filed February 13, 2004 amending claims 30, 31, 34 and 37 has been entered.

The Sequence Listing and the computer readable form thereof filed February 25, 2004 have been entered.

"Accompanying Statement to support filing and submission of corrected sequence listing in accordance with 37 C.F.R. §§ 1.821-1.825" signed by attorney Kendrew Colton has been entered.

Claims 1-9 and 11-41 are pending. Claims 15-38 are withdrawn (Office action mailed November 19, 2003, page 3).

Claims 1-9, 11-14 and 39-41 are under consideration.

Claim Objections

Claims 1-9, 11-14 and 39-41 are objected to because of the following informalities.

Claim 1 recites a Markush group of "A polynucleotide sequence". However claim 1 d) recites "polynucleotide". It is suggested that applicants maintain consistency throughout the claims and refer to either polynucleotide or polynucleotide sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11-14, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9, 11-14 recite "a polynucleotide coding for an enzyme capable of converting oxidized β-nicotinamide-adenine dinucleotide phosphate into a reduced form, wherein enzyme is glucose dehydrogenase". The genus of polynucleotides encoding a glucose dehydrogenase encompasses polynucleotides encoding glucose dehydrogenases having different structures and substrates and stereo specificities.

Claims 40 and 41 depend from claim 9 and claim 14, respectively, and limit glucose dehydrogenase to glucose dehydrogenase derived from *Bacillus megaterium*.

The specification does not disclose the number of glucose dehydrogenases in *Bacillus megaterium*. Furthermore, different strains of *Bacillus megaterium* may have glucose dehydrogenases with different structures and properties. The specification discloses only a single species of the claimed genus, a DNA encoding glucose dehydrogenase from *Bacillus megaterium* IFO12108. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of "coding for glucose dehydrogenase" and fails

to provide any structure: function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-9, 11-14 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide coding for SEQ ID NO:1, including SEQ ID NO:2 and a polynucleotide that hybridizes thereto under highly stringent conditions recited in claim 1 and encodes an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate, does not reasonably provide enablement for a polynucleotide sequence having 80% or more sequence identity with the polynucleotide sequence coding for an amino acid sequence of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Polynucleotide sequences having 80% or more sequence identity with the polynucleotide sequence coding for an amino acid sequence of SEQ ID NO:1 include a) sequences encoding an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate and b) sequences encoding polypeptides having no disclosed function. With regard to polynucleotide sequences encoding an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate, the specification teaches a polynucleotide of SEQ ID NO:2 coding for an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate from *Penicillium citrinum* IFO4631 having the amino acid sequence of SEQ ID NO:1.

The specification does not support the broad scope of the claims which encompass polynucleotide sequences having 80% or more sequence identity with the polynucleotide sequence coding for an amino acid sequence of SEQ ID NO:1 coding for an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting

the requisite activity; (B) the general tolerance of a protein capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues of a protein capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The specification does not provide information regarding other combinations of substitute amino acids that would result in a mutant enzyme retaining the requisite enzymatic activity. While there is a great number of possible mutants, it is *a priori* unpredictable as to which mutant will exhibit the claimed activity. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity or any other activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where the expectation of obtaining similar activity or any other activity is unpredictable based on the instant disclosure. Thus, with regard to polynucleotide sequences having 80% or more sequence identity with the

polynucleotide sequence coding for an amino acid sequence of SEQ ID NO:1 and coding for a polypeptide with an undisclosed function, the specification provides no guidance as to how to use said polynucleotide sequences.

Therefore, one of ordinary skill would require guidance, beyond that provides in the specification in order to make a polynucleotide with 80% or more sequence identity with the polynucleotide sequence coding for SEQ ID NO:1, said polynucleotide coding for an enzyme capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate and in order to use a polynucleotide sequence having 80% or more sequence identity with the polynucleotide sequence coding for SEQ ID NO:1 and coding for a polypeptide with an undisclosed function in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-14 and 39-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, with dependent claims 2-9, 11-14, 39-41, recites "an amino acid sequence of SEQ ID NO:1 having additional 6 amino acids". Said sequence is not SEQ ID NO:1 but a different sequence comprising SEQ ID NO:1.

Claim 1 is confusing because it recites a polynucleotide sequence that hybridizes under ... to a polynucleotide sequence encoding an amino acid sequence of SEQ ID

NO:1, the amino acid sequence being an amino acid sequence of an enzyme. SEQ ID NO:1 is the amino acid of said enzyme. Amending the claim to recite "a polynucleotide coding for an enzyme capable of ..., wherein said polynucleotide sequence hybridizes under ... to a polynucleotide sequence encoding SEQ ID NO:1", for example, is suggested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. A polynucleotide of SEQ ID NO:2 encoding a protein capable of preferentially producing (S)-4-bromo-3-hydroxy butanoate by asymmetrically reducing 4-bromo-3-oxobutanoate of SEQ ID NO:1 naturally occurs in *Penicillium citrinum*.

As the products of Nature, it is unpatentable. Amending claim 1 to recite, for example, " an isolated polynucleotide" is suggested.

Applicants did not amend the preamble or all clauses but only a single clause "c)".

Response to Arguments

With regard to the amended Sequence Listing Mr. Colton stated in "Accompanying Statement to support filing and submission of corrected sequence listing in accordance with 37 C.F.R. §§ 1.821-1.825", *supra*, that the amended sequences of SEQ ID NOs: 34 and 35 result from the re-sequencing of the deposit FERM BP-7752. The deposit was made prior to the earliest priority date of the instant application and is referenced in the specification as filed on page 23.

Applicant's arguments filed February 6, 2004 have been fully considered but they are not persuasive.

Applicants argue that "the requirement for restriction is acknowledged, as is the initial decision declining reconsideration. It is respectfully requested that the Examiner reconsider. The point is not whether this case is a PCT or the like, but rather whether a predicate for imposing the requirement for restriction has been undercut for the reasons of record" (Remarks, page 11).

This is not persuasive because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement.

Applicants do not explain the reasons for traversing the rejections but indicate support for the amendment (pages 12-13).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652